RESULTS. The cohort consisted of 1023 patients with DiGeorge syndrome. The mean age was 5.5 years and median age was 3.0 years; 855 patients had immunoglobulin data available. Overall, 19% (150 total) of patients had IgG levels <500 mg/dL; 6.2% (28 total) of patients older than 3 and 5.6% (19 total) older than 5 years had levels of IgG <500 mg/dL. A total of 7 patients had undetectable IgA levels (IgA = 0 mg/dL); ages ranged from 4 to 15 years with the mean age of 8.7 years. A total of 10 patients (1.3%) had measurable IgA levels <5 mg/dL; all were older than 3 years. Twenty-seven percent of patients (216 total) had IgM levels <40 mg/dL; 23% (104 total) of patients older than 3 years had IgM levels <40 mg/dL.

CONCLUSIONS. The investigators found that 3% of patients with DiGeorge syndrome were receiving immunoglobulin replacement therapy and 6% of patients older than 3 years had hypogammaglobulinemia. The investigators concluded that DiGeorge syndrome, which is typically thought of as a T-lymphocyte disorder, was associated with significant humoral immune deficiency.

REVIEWER COMMENTS. There has been a growing body of evidence that B-lymphocyte functional deficit and hypogammaglobulinemia are associated with more severe infections in DiGeorge syndrome. This investigation directly addresses this clinical issue and is the largest report to date of immunoglobulin levels in this patient population. The investigators clearly identified limitations of their registry approach to collect data. For example, the definition of DiGeorge syndrome was not uniform, the data sets were incomplete, and there may have been ascertainment bias in the overall analysis. Although imperfect, this registry approach was helpful in identifying an unexpectedly high frequency of humoral immune deficiency in patients with DiGeorge syndrome. A reasonable clinical strategy, as mentioned by the investigators, would be to measure IgG, IgA, and IgM levels and diphtheria and tetanus titers in immunized patients with DiGeorge syndrome with recurrent sinopulmonary infections. If humoral immunity is determined to be insufficient, additional beneficial therapies, such as immunoglobulin replacement therapy, should be considered.
nonimmune cells such as neurons are nonetheless essential for host defense against invading pathogens.

Conclusions. This study details the phenotypes and molecular investigation of the first reported patients with IL-21R deficiency, providing insight into the role of IL-21R in immune function. The poor clinical outcome of these patients highlights the importance of early primary immunodeficiency recognition, potentially enabling HSCT before development of irreversible secondary morbidities.

Reviewer Comments. As has been the case with previously discovered primary immunodeficiencies, this small case series reveals a glimpse into a specific aspect of immune function. In this case, we have learned that the IL-21R pathway is important for T- and B-cell responses protecting from respiratory and gastrointestinal infections, especially with Cryptosporidium. The case series also imparts the critical importance of identifying primary immunodeficiency early in life so that the best opportunity for successful HSCT can be provided.

Ribosomal Protein SA Haploinsufficiency in Humans With Isolated Congenital Asplenia


Purpose of the study. To identify a potential genetic basis for isolated congenital asplenia.

Study population. Thirty-three patients from 23 kindreds with a history of congenital asplenia, including multiplex kindreds that suggested an autosomal dominant inheritance pattern.

Methods. Genomic DNA was initially obtained from at least 1 member of each kindred and subjected to whole exome sequencing followed by testing of remaining subjects.

Results. Eighteen (55%) of the 33 subjects from 8 of the 21 kindreds were identified with 7 different heterozygous missense mutations of the gene encoding the ribosomal protein SA (RPSA). The mutations affect highly conserved nucleotides in mammals, vertebrates, and yeast and showed complete penetrance in that all individuals carrying the mutation had isolated congenital asplenia.

Conclusions. Heterozygous mutations in RPSA underlie all isolated congenital asplenia in the multiplex families studied (but not all subjects with isolated congenital asplenia). RPSA is involved in preribosomal processing, but its role in splenic development is unknown at this time. There were no other definable defects observed in these patients. Interestingly, another mutation affecting
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